STEROIDAL COMPOSITIONS CONTAINING HYDROXYCARBOXYLIC ACIDS AND METHODS OF USING THE SAME

FIELD OF THE INVENTION

The present inventive subject matter relates to pharmaceutical compositions suitable for topical administration comprising two active ingredients, a hydroxycarboxylic acid and prednicarbate, and a pyrrolidone carboxylate salt moisturizing agent. In a particular aspect, the two active ingredients in the present inventive compositions have a purity of at least 90% and a concentration of degradation product(s) less than about 10% of the starting concentration of the active ingredients. These compositions are used for topical medical applications, particularly to treat steroid responsive dermatoses.

BACKGROUND OF THE INVENTION

Topical medications that include corticosteroids are known in the art as useful for treating skin conditions such as atopic dermatitis, psoriasis and other pathologies of the skin. Current steroid-containing products are available mainly as gels, lotions or ointments that are supplied in tubes or bottles and applied to an affected area of the skin by hand.

However, the results of using corticosteroids in topical treatment of, for example, psoriasis have been variable and unpredictable. In some cases topical corticosteroids seemed to improve and eradicate the psoriatic lesions, but in other cases corticosteroids appeared to be ineffective on topical administration. Drug resistance and rebound worsening are also common features when corticosteriods alone are used in the treatment of psoriasis. Accordingly, it is often required to use corticosteroids in combination with another ingredient that stabilizes and enhances the activity of the corticosteroid.

U.S. Patent No. 3,879,537 describes the use of certain α-hydroxy acids, α-keto acids, and related compounds for topical treatment of fish-scale like ichthyotic conditions in humans.

Similarly, U.S. Patent No. 3,920,835 describes the use of these certain α-hydroxy acids, α-keto acids, and their derivatives for topical treatment of dandruff, acne, and palmar and plantar hyperkeratosis. α-hydroxy acids and α-keto acids, then, were also well known in the art as having dermatological effects.

In view of these prior teachings, U.S. Patent No. 4,246,261 discloses that hydroxy acids and related compounds greatly enhance the therapeutic efficacy of corticosteroids in the topical treatment of such

dermatological disorders as psoriasis, eczema, seborrheic dermatitis, and other inflammatory skin conditions.

A number of products have entered the marketplace taking advantage of this hydroxy acid-corticosteroid combination. For example, the Lacticare-HC Lotion product (Stiefel Laboratories, Inc., Coral Gables, FL) contains a combination of hydrocortisone and lactic acid. This product has been well known for use in the treatment of, for example, pruritis.

Numerous other similar products have entered the marketplace containing a combination of hydroxy acids such as lactic acid and a corticosteroid such as hydrocortisone. The majority of these products, however, contain hydrocortisone as the steroidal active ingredient.

Excessive use of hydrocortisone is well-known to exhibit a variety of undesired side effects, including blurred vision, halos around lights, an irregular heartbeat, insomnia, mood changes, weight gain, fatigue, redness, blistering, burning, itching, peeling, thinning of the skin, and stretch marks. Additionally, it is well known that children are especially sensitive to the unwanted side effects of topically administered hydrocortisone. Accordingly, there remains a need in the art for topical corticosteroid products containing a steroid other than hydrocortisone, especially for the

treatment of children.

Several such topical products containing a steroid other than hydrocortisone have been sold. However, none of these teach or suggest the use of a moisturizing agent which may aid in the therapeutic effects and patient compliance with these compositions. As shown by U.S. Patent No. 5,874,974 it is desirable to include an agent having a moisturizing or emollient effect with a composition containing a steroid to supplement the curative action of the steroid and to enhance the effect of the steroid on the skin.

One deficiency of the prior art topical steroid compositions is the lack of recognition for maintaining a high purity level of the active drugs with a low amount of degradates. This deficiency is overcome with the present formulations which not only contain three essential components but also require a high drug purity and low drug degradates, which increases the effectiveness and shelf-life of the topical composition.

Accordingly, there remains a need in the art for topical steroidal compositions useful in treating a variety of dermatological disorders that contain a steroid other than hydrocortisone, a second ingredient, such as a hydroxy acid, to stabilize and enhance the activity of the steroid, and a moisturizing agent to supplement the curative activity of the steroid. There

further remains a need for such topical compositions that maintain a high purity level of the active drug(s) and a low level of degradates thereof. The present inventive subject matter addresses these needs.

SUMMARY OF THE INVENTION

The present inventive subject matter relates to a pharmaceutical composition suitable for topical administration comprising:

about 1 to about 30% by weight of an α-hydroxy acid or a pharmaceutically acceptable salt thereof having a purity of at least 90% and a concentration of degradation product(s) less than about 10% of the starting concentration of said α-hydroxy acid;

about 0.05 to about 2.0% by weight of prednicarbate or a pharmaceutically acceptable salt thereof having a purity of at least 90% and a concentration of degradation product(s) less than about 10% of the starting concentration of said prednicarbate; and

about 0.5 to about 10% by weight of a pyrrolidone carboxylate salt.

In a preferred embodiment, the present inventive subject matter relates to a method of treating a steroid responsive dermatosis in a mammal, comprising topically administering to a mammal in need thereof a therapeutically effective amount of a pharmaceutical

composition suitable for topical administration comprising:

about 1 to about 30% by weight of an α-hydroxy acid or a pharmaceutically acceptable salt thereof having a purity of at least 90% and a concentration of degradation product(s) less than about 10% of the starting concentration of said α-hydroxy acid;

about 0.05 to about 2.0% by weight of prednicarbate or a pharmaceutically acceptable salt thereof having a purity of at least 90% and a concentration of degradation product(s) less than about 10% of the starting concentration of said prednicarbate; and

about 0.5 to about 10% by weight of a pyrrolidone carboxylate salt.

In another preferred embodiment, the present inventive subject matter relates to a method of treating diseased tissue in a mammal, comprising topically administering to said diseased tissue a therapeutically effective amount of a pharmaceutical composition suitable for topical administration comprising:

about 1 to about 30% by weight of an α-hydroxy acid or a pharmaceutically acceptable salt thereof having a purity of at least 90% and a concentration of degradation product(s) less than about 10% of the starting concentration of said α-hydroxy acid;

about 0.05 to about 2.0% by weight of prednicarbate

or a pharmaceutically acceptable salt thereof having a purity of at least 90% and a concentration of degradation product(s) less than about 10% of the starting concentration of said prednicarbate; and

about 0.5 to about 10% by weight of a pyrrolidone carboxylate salt.

In yet another preferred embodiment, the present inventive subject matter relates to use of prednicarbate or a pharmaceutically acceptable salt thereof for the preparation of a topical pharmaceutical composition comprising:

about 1 to about 30% by weight of an α-hydroxy acid or a pharmaceutically acceptable salt thereof having a purity of at least 90% and a concentration of degradation product(s) less than about 10% of the starting concentration of said α-hydroxy acid;

about 0.05 to about 2.0% by weight of prednicarbate or a pharmaceutically acceptable salt thereof having a purity of at least 90% and a concentration of degradation product(s) less than about 10% of the starting concentration of said prednicarbate; and

about 0.5 to about 10% by weight of a pyrrolidone carboxylate salt

for treating a steroid responsive dermatosis in a patient.

In still another preferred embodiment, the present

inventive subject matter relates to use of prednicarbate or a pharmaceutically acceptable salt thereof for the preparation of a topical pharmaceutical composition comprising:

about 1 to about 30% by weight of an α-hydroxy acid or a pharmaceutically acceptable salt thereof having a purity of at least 90% and a concentration of degradation product(s) less than about 10% of the starting concentration of said α-hydroxy acid;

about 0.05 to about 2.0% by weight of prednicarbate or a pharmaceutically acceptable salt thereof having a purity of at least 90% and a concentration of degradation product(s) less than about 10% of the starting concentration of said prednicarbate; and

about 0.5 to about 10% by weight of a pyrrolidone carboxylate salt

for treating diseases tissue in a patient.

In a further preferred embodiment, the present inventive subject matter relates to pharmaceutical composition suitable for topical administration comprising an emulsion comprising:

an oil phase comprising an oily material selected from the group consisting of mineral oil, petrolatum, petroleum derivatives, fatty acids, fatty acid derivatives, fatty alcohols, fatty alcohol derivatives, paraffins, and mixtures thereof and at least two

emulsifiers;

an aqueous phase comprising about 1 to about 10% by weight of an α-hydroxy acid or a pharmaceutically acceptable salt thereof having a purity of at least 90% and a concentration of degradation product(s) less than about 10% of the starting concentration of said α-hydroxy acid and about 1 to about 8% by weight of a pyrrolidone carboxylate salt; and

about 0.1 to about 1.0% by weight of prednicarbate or a pharmaceutically acceptable salt thereof having a purity of at least 90% and a concentration of degradation product(s) less than about 10% of the starting concentration of said prednicarbate dispersed throughout said emulsion,

wherein said pharmaceutical composition has a pH of from about 3.0 to about 6.0.

In still yet another preferred embodiment, the present inventive subject matter relates to a method of treating a steroid responsive dermatosis in a mammal, comprising administering to a mammal in need thereof a therapeutically effective amount of a pharmaceutical composition suitable for topical administration comprising an emulsion comprising:

an oil phase comprising an oily material selected from the group consisting of mineral oil, petrolatum, petroleum derivatives, fatty acids, fatty acid

derivatives, fatty alcohols, fatty alcohol derivatives, paraffins, and mixtures thereof and at least two emulsifiers;

an aqueous phase comprising about 1 to about 10% by weight of an α-hydroxy acid or a pharmaceutically acceptable salt thereof having a purity of at least 90% and a concentration of degradation product(s) less than about 10% of the starting concentration of said α-hydroxy acid and about 1 to about 8% by weight of a pyrrolidone carboxylate salt; and

about 0.1 to about 1.0% by weight of prednicarbate or a pharmaceutically acceptable salt thereof having a purity of at least 90% and a concentration of degradation product(s) less than about 10% of the starting concentration of said prednicarbate dispersed throughout said emulsion,

wherein said pharmaceutical composition has a pH of from about 3.0 to about 6.0.

In yet another preferred embodiment, the present inventive subject matter relates to a method of treating diseased tissue in a mammal, comprising topically administering to said diseases tissue a therapeutically effective amount of a pharmaceutical composition suitable for topical administration comprising an emulsion comprising:

an oil phase comprising an oily material selected

from the group consisting of mineral oil, petrolatum, petroleum derivatives, fatty acids, fatty acid derivatives, fatty alcohols, fatty alcohol derivatives, paraffins, and mixtures thereof and at least two emulsifiers;

an aqueous phase comprising about 1 to about 10% by weight of an α-hydroxy acid or a pharmaceutically acceptable salt thereof having a purity of at least 90% and a concentration of degradation product(s) less than about 10% of the starting concentration of said α-hydroxy acid and about 1 to about 8% by weight of a pyrrolidone carboxylate salt; and

about 0.1 to about 1.0% by weight of prednicarbate or a pharmaceutically acceptable salt thereof having a purity of at least 90% and a concentration of degradation product(s) less than about 10% of the starting concentration of said prednicarbate dispersed throughout said emulsion,

wherein said pharmaceutical composition has a pH of from about 3.0 to about 6.0.

In yet another further preferred embodiment, the present inventive subject matter relates to use of an α-hydroxy acid or a pharmaceutically acceptable salt thereof for the preparation of a topical pharmaceutical composition comprising an emulsion comprising:

an oil phase comprising an oily material selected

from the group consisting of mineral oil, petrolatum, petroleum derivatives, fatty acids, fatty acid derivatives, fatty alcohols, fatty alcohol derivatives, paraffins, and mixtures thereof and at least two emulsifiers;

an aqueous phase comprising about 1 to about 10% by weight of an α-hydroxy acid or a pharmaceutically acceptable salt thereof having a purity of at least 90% and a concentration of degradation product(s) less than about 10% of the starting concentration of said α-hydroxy acid and about 1 to about 8% by weight of a pyrrolidone carboxylate salt; and

about 0.1 to about 1.0% by weight of prednicarbate or a pharmaceutically acceptable salt thereof having a purity of at least 90% and a concentration of degradation product(s) less than about 10% of the starting concentration of said prednicarbate dispersed throughout said emulsion,

wherein said pharmaceutical composition has a pH of from about 3.0 to about 6.0

for treating a steroid responsive dermatosis in a patient.

In another preferred embodiment, the present inventive subject matter further relates to use of an α-hydroxy acid or a pharmaceutically acceptable salt thereof for the preparation of a topical pharmaceutical

composition comprising an emulsion comprising:

an oil phase comprising an oily material selected from the group consisting of mineral oil, petrolatum, petroleum derivatives, fatty acids, fatty acid derivatives, fatty alcohols, fatty alcohol derivatives, paraffins, and mixtures thereof and at least two emulsifiers;

an aqueous phase comprising about 1 to about 10% by weight of an α-hydroxy acid or a pharmaceutically acceptable salt thereof having a purity of at least 90% and a concentration of degradation product(s) less than about 10% of the starting concentration of said α-hydroxy acid and about 1 to about 8% by weight of a pyrrolidone carboxylate salt; and

about 0.1 to about 1.0% by weight of prednicarbate or a pharmaceutically acceptable salt thereof having a purity of at least 90% and a concentration of degradation product(s) less than about 10% of the starting concentration of said prednicarbate dispersed throughout said emulsion,

wherein said pharmaceutical composition has a pH of from about 3.0 to about 6.0

for treating diseased tissue in a patient.

In yet another particularly preferred embodiment, the present inventive subject matter relates to a process for preparing a pharmaceutical composition suitable for

topical administration comprising an emulsion, said process comprising:

1) preparing an oil phase comprising an oily material selected from the group consisting of mineral oil, petrolatum, petroleum derivatives, fatty acids, fatty acid derivatives, fatty alcohols, fatty alcohol derivatives, paraffins, and mixtures thereof and at least two emulsifiers;

2) preparing an aqueous phase comprising an α-hydroxy acid or a pharmaceutically acceptable salt thereof having a purity of at least 90% and a concentration of degradation product(s) less than about 10% of the starting concentration of said α-hydroxy acid and a pyrrolidone carboxylate salt;

3) adjusting the pH of said aqueous phase to a range of about 3.0 to about 6.0.

4) adding said oil phase to said aqueous phase while mixing at a temperature of about 55 to about 85 ^{0}C to obtain a homogenous emulsion;

5) cooling said emulsion to a temperature of about 25 to about 45 ^{0}C;

6) solubilizing prednicarbate or a pharmaceutically acceptable salt thereof having a purity of at least 90% and a concentration of degradation product(s) less than about 10% of the starting concentration of said prednicarbate in a lower

alkyl alcohol and dispersing said prednicarbate throughout said emulsion; and

7) recovering a topical emulsion pharmaceutical composition.

In still another preferred embodiment, the present inventive subject matter relates to pharmaceutical composition suitable for topical administration comprising:

about 1 to about 30% by weight of lactic acid or a pharmaceutically acceptable salt thereof;

about 0.05 to about 2.0% by weight of prednicarbate or a pharmaceutically acceptable salt thereof; and

about 0.5 to about 10% by weight of sodium pyrrolidone carboxylate.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

As used herein, "degradation products" refers to the product(s) produced by decomposition of one or more of the active ingredients of the present inventive compositions.

As used herein, an "extended period of time" refers to the shelf life of a composition of the present inventive subject matter, including time spent on the shelf at a pharmacy as well as the entire time period after sale of the composition during which the

composition remains effective for the indicated use.

As used herein, "lactones" refers to derivatives of the subject compound(s), modified so that a hydroxyl group and a carboxylic acid group combine to form a cyclic ester, that possess the same pharmacological activity as the subject compound(s) and which are neither biologically nor otherwise undesirable. Non-limiting examples of suitable lactones include gluconolactone, galactonolactone, glucuronolactone, galacturonolactone, gulonolactone, ribonolactone, saccharic acid lactone, pantoyllactone, glucoheptonolactone, mannonolactone, and galactoheptonolactone.

As used herein, "pharmaceutically acceptable salts " refers to salts of the active compound(s) which possess the same pharmacological activity as the active compound(s) and which are neither biologically nor otherwise undesirable. A salt can be formed with, for example, organic or inorganic acids. Non-limiting examples of suitable acids include acetic acid, acetylsalicylic acid, adipic acid, alginic acid, ascorbic acid, aspartic acid, benzoic acid, benzenesulfonic acid, bisulfic acid, boric acid, butyric acid, camphoric acid, camphorsulfonic acid, carbonic acid, citric acid, cyclopentanepropionic acid, digluconic acid, dodecylsulfic acid, ethanesulfonic acid, formic acid, fumaric acid, glyceric acid, glycerophosphoric acid,

glycine, glucoheptanoic acid, gluconic acid, glutamic acid, glutaric acid, glycolic acid, hemisulfic acid, heptanoic acid, hexanoic acid, hippuric acid, hydrobromic acid, hydrochloric acid, hydroiodic acid, hydroxyethanesulfonic acid, lactic acid, maleic acid, malic acid, malonic acid, mandelic acid, methanesulfonic acid, mucic acid, naphthylanesulfonic acid, naphthylic acid, nicotinic acid, nitrous acid, oxalic acid, pelargonic, phosphoric acid, propionic acid, saccharin, salicylic acid, sorbic acid, succinic acid, sulfuric acid, tartaric acid, thiocyanic acid, thioglycolic acid, thiosulfuric acid, tosylic acid, undecylenic acid, ethanolamine, naturally and synthetically derived amino acids. Non-limiting examples of base salts include ammonium salts; alkali metal salts, such as sodium and potassium salts; alkaline earth metal salts, such as calcium and magnesium salts; salts with organic bases, such as dicyclohexylamine salts; methyl-D-glucamine; and salts with amino acids, such as arginine, lysine, and so forth. Also, the basic nitrogen-containing groups can be quaternized with such agents as lower alkyl halides, such as methyl, ethyl, propyl, and butyl chlorides, bromides, and iodides; dialkyl sulfates, such as dimethyl, diethyl, dibutyl, and diamyl sulfates; long chain halides, such as decyl, lauryl, myristyl, and stearyl chlorides, bromides, and iodides; asthma halides, such as benzyl and phenethyl

bromides; and others. Water or oil-soluble or dispersible products are thereby obtained.

Other terms as used herein are meant to be defined by their well-known meanings in the art.

Topical Pharmaceutical Compositions

The present inventive subject matter pertains to a pharmaceutical composition suitable for topical administration comprising:

about 1 to about 30% by weight of an α-hydroxy acid or a pharmaceutically acceptable salt thereof having a purity of at least 90% and a concentration of degradation product(s) less than about 10% of the starting concentration of said α-hydroxy acid;

about 0.05 to about 2.0% by weight of prednicarbate or a pharmaceutically acceptable salt thereof having a purity of at least 90% and a concentration of degradation product(s) less than about 10% of the starting concentration of said prednicarbate; and

about 0.5 to about 10% by weight of a pyrrolidone carboxylate salt.

The present inventive pharmaceutical compositions suitable for topical administration contain two active ingredients: an α-hydroxy acid and prednicarbate. The presence of these two different active ingredients conveys a synergistic, or a greater than additive, effect upon application of the present inventive compositions to

the skin. That is, the present inventive compositions containing both of these active ingredients produce a greater medical effect than would be exhibited by adding the medical effects of an α-hydroxy acid and prednicarbate applied to the same skin separately.

Additionally, the present inventive pharmaceutical compositions contain a moisturizing agent, preferably a pyrrolidone carboxylate salt moisturizing agent. This moisturizing agent acts to further enhance the effects and curative action of the prednicarbate on the skin. Further, the moisturizing agent moisturizes the skin, avoiding normal side effects of corticosteroid use such as drying, redness, blistering, burning, itching, and peeling of the skin. Accordingly, the addition of the moisturizing agent to the present compositions will improve patient compliance with a prescribed treatment regimen.

The present inventive compositions are preferably formed as an oil-in-water emulsion, i.e. an emulsion having an oil phase and an aqueous phase. Preferably, the oil phase of the emulsion comprises an oily material and an emulsifier to aid in formation of the emulsion. More preferably, the oil phase contains at least two emulsifiers.

The first active ingredient, α-hydroxy acid or pharmaceutically acceptable salt thereof, is preferably

contained in the aqueous phase of the emulsion. The aqueous phase additionally preferably contains the moisturizing agent of the present inventive compositions, i.e. the pyrrolidone carboxylate salt. The pH of this aqueous phase, if required, is adjusted to a range of about 3.0 to about 6.0 before it is combined with the oil phase to form the emulsion. In a particularly preferred embodiment, the pH of the aqueous phase is adjusted to a pH range of about 4.0 to about 5.0.

Once the oil phase and the aqueous phase are combined to form the emulsion, the second active ingredient, prednicarbate or a pharmaceutically acceptable salt thereof, is solubilized in a suitable solvent and dispersed throughout the emulsion.

Since the emulsion is an oil-in-water emulsion having water as the major component, the final composition will have a pH mirroring that of the aqueous phase. Accordingly, the pH of the final composition preferably ranges from about 3.0 to about 6.0. In a particularly preferred embodiment, the pH of the final composition ranges from about 4.0 to about 5.0.

These particular emulsion and pH characteristics convey to the present compositions the unique advantages of being able to maintain a high purity level and a low concentration of degradation products of the active ingredients. The high purity level and low concentration

of degradation products permits the present inventive compositions to have a longer shelf life and increased pharmaceutical effectiveness when compared with other corticosteroid products previously known in the art.

In this regard, the present inventive compositions maintain a purity level of at least 90%, preferably at least 92.5%, more preferably at least 95% of each of the active ingredients over an extended period of time.

Likewise, the present inventive compositions are able to maintain a low concentration of degradation product(s) of the active ingredients over an extended period of time. In this regard, the present compositions will maintain a concentration of degradation product(s) less than about 10%, preferably less than about 7.5%, more preferably less than about 5% of the starting concentration of each of the active ingredients. These advantageous properties were previously unknown in the prior art compositions.

α-Hydroxy Acids

The present inventive compositions preferably contain about 1 to about 30% by weight of an α-hydroxy acid or a pharmaceutically acceptable salt thereof as a first active ingredient. In a particularly preferred embodiment, the present inventive compositions contain about 1 to about 10% by weight of the α-hydroxy acid or a pharmaceutically acceptable salt thereof. In a most

preferred embodiment, the present inventive compositions contain about 3 to about 7% by weight of the α-hydroxy acid or a pharmaceutically acceptable salt thereof.

It is an essential aspect for the present inventive compositions to maintain a purity level of at least 90%, preferably at least 92.5%, more preferably at least 95% of the α-hydroxy acid over an extended period of time. Likewise, the present inventive compositions are able to maintain a low concentration of degradation product(s) of the α-hydroxy acid, namely less than about 10%, preferably less than about 7.5%, more preferably less than about 5% of the starting concentration of the α-hydroxy acid over an extended period of time.

The α-hydroxy acids useful in the present inventive compositions are organic carboxylic acids in which one hydroxyl group is attached to the alpha carbon of the acids. The generic structure of such alpha hydroxyacids may be represented as follows:

$$(R_a)(R_b)C(OH)COOH$$

where R_a and R_b each independently are an H, F, Cl, Br, alkyl, aralkyl, or aryl group of saturated or unsaturated, isomeric or non-isomeric, straight or branched chain or cyclic form, having 1 to 25 carbon atoms. In addition R_a and R_b may each carry one or more OH, CHO, COOH, or alkoxy groups having 1 to 9 carbon atoms. The α-hydroxy acids may exist as stereoisomers as

D, L, and DL forms when R_a and R_b are not identical.

The α-hydroxy acid may be present in the inventive compositions as a free acid, in lactone form, or in a salt form with an organic base or an inorganic alkali. In a preferred embodiment, the α-hydroxy acid is present in the inventive compositions as a mixture of an acid and a salt.

Typical alkyl, aralkyl and aryl groups for R_a and R_b include methyl, ethyl, propyl, isopropyl, butyl, pentyl, octyl, lauryl, stearyl, benzyl, and phenyl, etc. These α-hydroxy acids may be divided into the following non-limiting exemplary groups: (1) alkyl α-hydroxy acids, (2) aralkyl and aryl α-hydroxy acids, (3) polyhydroxy α-hydroxy acids, and (4) polycarboxylic α-hydroxy acids. The following are representative, non-limiting examples of α-hydroxy acids in each subgroup.

(1) Alkyl α-hydroxy acids

1. 2-Hydroxyethanoic acid (Glycolic acid, hydroxyacetic acid)

(H)(H)C(OH)COOH

2. 2-Hydroxypropanoic acid (Lactic acid)

(CH_3)(H)C(OH)COOH

3. 2-Methyl 2-hydroxypropanoic acid (Methyllactic acid)

$(CH_3)(CH_3)$C(OH)COOH

4. 2-Hydroxybutanoic acid

$(C_2H_5)(H)C(OH)COOH$

5. 2-Hydroxypentanoic acid

$(C_3H_7)(H)C(OH)COOH$

6. 2-Hydroxyhexanoic acid

$(C_4H_9)(H)C(OH)COOH$

7. 2-Hydroxyheptanoic acid

$(C_5H_{11})(H)C(OH)COOH$

8. 2-Hydroxyoctanoic acid

$(C_6H_{13})(H)C(OH)COOH$

9. 2-Hydroxynonanoic acid

$(C_7H_{15})(H)C(OH)COOH$

10. 2-Hydroxydecanoic acid

$(C_8H_{17})(H)C(OH)COOH$

11. 2-Hydroxyundecanoic acid

$(C_9H_{19})(H)C(OH)COOH$

12. 2-Hydroxydodecanoic acid (Alpha hydroxylauric acid)

$(C_{10}H_{21})(H)C(OH)COOH$

13. 2-Hydroxytetradecanoic acid (Alpha hydroxymyristic acid)

$(C_{12}H_{25})(H)C(OH)COOH$

14. 2-Hydroxyhexadecanoic acid (Alpha hydroxypalmitic acid)

$(C_{14}H_{29})(H)C(OH)COOH$

15. 2-Hydroxyoctadecanoic acid (Alpha hydroxystearic acid)

$(C_{16}H_{34})(H)C(OH)COOH$

16. 2-Hydroxyeicosanoic acid (Alpha hydroxyarachidonic acid)

$(C_{18}H_{37})(H)C(OH)COOH$

(2) Aralkyl And Aryl α-hydroxy acids

1. 2-Phenyl 2-hydroxyethanoic acid (Mandelic acid)

$(C_6H_5)(H)C(OH)COOH$

2. 2,2-Diphenyl 2-hydroxyethanoic acid (Benzilic acid)

$(C_6H_5)(C_6H_5)C(OH)COOH$

3. 3-Phenyl 2-hydroxypropanoic acid (Phenyllactic acid)

$(C_6H_5CH_2)(H)C(OH)COOH$

4. 2-Phenyl 2-methyl 2-hydroxyethanoic acid (Atrolactic acid)

$(C_6H_5)(CH_3)C(OH)COOH$

5. 2-(4'-Hydroxyphenyl) 2-hydroxyethanoic acid (4-Hydroxymandelic acid)

$(HO\text{-}C_6H_4)(H)C(OH)COOH$

6. 2-(4'-Chlorophenyl) 2-hydroxyethanoic acid (4-Chloromandelic acid)

$(Cl\text{-}C_6H_4)(H)C(OH)COOH$

7. 2-(3'-Hydroxy-4'-methoxyphenyl) 2-hydroxyethanoic acid (3-Hydroxy-4-methoxymandelic acid)

$(HO\text{-},CH_3O\text{-}C_6H_3)(H)C(OH)COOH$

8. 2-(4'-Hydroxy-3'-methoxyphenyl) 2-hydroxyethanoic

acid (4-Hydroxy-3-methoxymandelic acid)

$(HO-,CH_3O-C_6H_3)(H)C(OH)COOH$

9. 3-(2'-Hydroxyphenyl) 2-hydroxypropanoic acid [3-(2'-Hydroxyphenyl) lactic acid]

$HO-C_6H_4-CH_2(H)C(OH)COOH$

10. 3-(4'-Hydroxyphenyl) 2-hydroxypropanoic acid [3-(4'-Hydroxyphenyl) lactic acid]

$HO-C_6H_4-CH_2(H)C(OH)COOH$

11. 2-(3',4'-Dihydroxyphenyl) 2-hydroxyethanoic acid (3,4-Dihydroxymandelic acid)

$HO-,HO-C_6H_3(H)C(OH)COOH$

(3) Polyhydroxy α-hydroxy acids

1. 2,3-Dihydroxypropanoic acid (Glyceric acid)

$(HOCH_2)(H)C(OH)COOH$

2. 2,3,4-Trihydroxybutanoic acid (Isomers; erythronic acid, threonic acid)

$HOCH_2(HO)CH_2(H)C(OH)COOH$

3. 2,3,4,5-Tetrahydroxypentanoic acid (Isomers; ribonic acid, arabinoic acid, xylonic acid, lyxonic acid)

$HOCH_2(HO)CH_2(HO)CH_2(H)C(OH)COOH$

4. 2,3,4,5,6-Pentahydroxyhexanoic acid (Isomers; allonic acid, altronic acid, gluconic acid, mannoic acid, gulonic acid, idonic acid, galactonic acid, talonic acid)

$HOCH_2(HO)CH_2(HO)CH_2(HO)CH_2(H)C(OH)COOH$

5. 2,3,4,5,6,7-Hexahydroxyheptanoic acid (Isomers; glucoheptonic acid, galactoheptonic acid etc.)

$HOCH_2(HO)CH_2(HO)CH_2(HO)CH_2(HO)CH_2(H)C(OH)COOH$

(4) Polycarboxylic α-hydroxy acids

1. 2-Hydroxypropane-1,3-dioic acid (Tartronic acid)

$HOOC(H)C(OH)COOH$

2. 2-Hydroxybutane-1,4-dioic acid (Malic acid)

$HOOCCH_2(H)C(OH)COOH$

3. 2,3-Dihydroxybutane-1,4-dioic acid (Tartaric acid)

$HOOC(HO)CH(H)C(OH)COOH$

4. 2-Hydroxy-2-carboxypentane-1,5-dioic acid (Citric acid)

$HOOCCH_2C(OH)(COOH)CH_2COOH$

5. 2,3,4,5-Tetrahydroxyhexane-1,6-dioic acid (Isomers; saccharic acid, mucic acid etc.)

$HOOC(CHOH)_4COOH$

Particularly preferred α-hydroxy acids useful in the present inventive compositions are those selected from the group consisting of atrolactic acid, benzilic acid, 4-chloromandelic acid, citric acid, 3,4-dihydroxymandelic acid, ethyl pyruvate, galacturonic acid, gluconolactone, glucuronic acid, glucuronolactone, glycolic acid, 2-hydroxybutanoic acid, 2-hydroxypentanoic acid, 2-hydroxyhexanoic acid, 2-hydroxyheptanoic acid, 2-hydroxyactanoic acid, 2-hydroxynonanoic acid, 2-

hydroxydecanoic acid, 2-hydroxyundecanoic acid, 4-hydroxymandelic acid, 3-hydroxy-4-methoxymandelic acid, 4-hydroxy-3-methoxymandelic acid, α-hydroxyarachidonic acid, α-hydroxybutyric acid, α-hydroxyisobutyric acid, α-hydroxylauric acid, α-hydroxymyristic acid, α-hydroxypalmitic acid, α-hydroxystearic acid, 3-(2'-hydroxyphenyl)lactic acid, 3-(4'-hydroxyphenyl)lactic acid, lactic acid, malic acid, mandelic acid, methyllactic acid, methylpyruvate, mucic acid, α-phenylactic acid, α-phenylpyruvic acid, pyruvic acid, saccharic acid, tartaric acid, tartronic acid, pharmaceutically acceptable salts thereof, and mixtures thereof.

In a most preferred embodiment, the α-hydroxy acid is lactic acid or a salt thereof.

Prednicarbate

The present inventive compositions further contain about 0.05 to about 2.0% by weight of the steroid prednicarbate or a pharmaceutically acceptable salt thereof as a second active ingredient. In a particularly preferred embodiment, the present inventive compositions contain about 0.1 to about 1.0% by weight of the prednicarbate or a pharmaceutically acceptable salt thereof. In a most preferred embodiment, the present inventive compositions contain about 0.15 to about 0.5% by weight of the prednicarbate or a pharmaceutically

acceptable salt thereof.

It is an essential aspect for the present inventive compositions to maintain a purity level of at least 90%, preferably at least 92.5%, more preferably at least 95% of the prednicarbate over an extended period of time. Likewise, the present inventive compositions are able to maintain a low concentration of degradation product(s) of the prednicarbate, e.g. less than about 10%, preferably less than about 7.5%, more preferably less than about 5% of the starting concentration of the prednicarbate, over an extended period of time.

Prednicarbate is especially useful in the present inventive compositions since children and those having sensitive skin more easily tolerate it than other known steroids, such as hydrocortisone. Accordingly, by virtue of the presence of prednicarbate rather than hydrocortisone, the present inventive compositions permit a greater frequency of administration and a greater amount of drug to be delivered to children and those with sensitive skin.

However, it is further contemplated as within the scope of the presently claimed invention that another steroid may be used as a substitute for the prednicarbate so long as the other steroid maintains a purity level of at least 90% and a concentration of degradation product(s) less than about 10% over an extended period of

time. Additionally, the other steroid must be easier tolerated by children and those with sensitive skin than is hydrocortisone.

Non-limiting examples of such substitute steroids include desonide, triamcinolone acetonide, betamethasone valerate, betamethasone dipropionate, betamethasone benzoate, clobetasol propionate, halcinonide, desoximethasone, amcinonide, fluocinonide, fluandrenolide, alclometasone dipropionate, fluocinolone acetonide, diflorasone diacetate, mometasone furoate, fluorometholone, clocortolone pivalate, halcinonide, and the like.

Moisturizing Agents

The present inventive compositions further contain as an essential component a moisturizing agent, preferably about 0.5 to about 10% by weight of a pyrrolidone carboxylate salt as a moisturizing agent. In a particularly preferred embodiment, the present inventive compositions contain about 1 to about 8% by weight of the pyrrolidone carboxylate salt. In a most preferred embodiment, the present inventive compositions contain about 3 to about 7% by weight of the pyrrolidone carboxylate salt.

Preferred non-limiting examples of pyrrolidone carboxylate salts useful in the present inventive compositions include sodium, potassium, chitosan,

magnesium, calcium, strontium, and lithium pyrrolidone carboxylate. A particularly preferred salt in this regard is sodium pyrrolidone carboxylate.

It is further contemplated as within the scope of the presently claimed invention that other moisturizing agents known to those of ordinary skill in the topical pharmaceutical arts may be used as a substitute for the pyrrolidone carboxylate salt. Non-limiting examples of such substitute moisturizing agents include C_3-C_6 diols and triols, glycerin, sorbitol, propylene glycol, dipropylene glycol, 1,3-butylene glycol, glucose, xylitol, maltitol, polyethylene glycol, hyaluronic acid, chondroitin sulfuric acid, polyoxyethylene methylglycoside, and polyoxypropylene methylglycoside.

The addition of the moisturizing agent to the present inventive pharmaceutical compositions enhances the effects and curative action of the prednicarbate on the skin. Further, the moisturizing agent moisturizes the skin, avoiding normal side effects of corticosteroid use such as drying, redness, blistering, burning, itching, and peeling of the skin. Accordingly, the addition of the moisturizing agent to the present compositions will improve patient compliance with a prescribed treatment regimen.

Additional Ingredients

The present inventive compositions are preferably

formed as an oil-in-water emulsion having an oil phase and an aqueous phase. In this regard, the oil phase of the emulsion comprises an oily material and at least one emulsifier to aid in formation of the emulsion.

Non-limiting exemplary oily materials include mineral oil, petrolatum, petroleum derivatives, fatty acids, fatty acid derivatives, fatty alcohols, fatty alcohol derivatives, paraffins, and mixtures thereof.

At least one emulsifier is used in the present inventive compositions to form the emulsion. In a preferred embodiment, at least two emulsifiers are present in the oil phase to help form the emulsion. Preferred, non-limiting examples of emulsifiers used in the present inventive compositions include polyoxyethylene sorbitan fatty acid esters, sorbitan fatty acid esters, propylene glycol stearate, glyceryl monostearate, polyethylene glycol, fatty alcohols, polymeric ethylene oxide-propylene oxide block polymers (Pluronics), derivatives thereof, pharmaceutically acceptable salts thereof, and mixtures thereof. In a preferred embodiment, the emulsifiers used in the present inventive compositions are either naturally or synthetically prepared.

Particularly preferred emulsifies useful in the present inventive compositions include but are not limited to stearyl alcohol and polyoxyethylene(20)

cetostearyl ether (Ceteareth-20), and glyceryl stearate and polyethyleneglycol-100 (PEG-100)/glyceryl stearate.

The aqueous phase forms the major portion of the present emulsion compositions. Accordingly, the present compositions preferably comprise about 50 to about 98% by weight water. In a particularly preferred embodiment, the present compositions comprise about 55 to about 85% by weight water.

The present inventive compositions may further comprise several additional excipients commonly known to those of ordinary skill in the art as useful in topical compositions. Several non-limiting examples of such additional excipients include antioxidants, chelates, preservatives, emollients, humectants, fluid alkyl alcohols, thickening agents, pH modifier, and mixtures thereof.

Non-limiting examples of specific antioxidants useful in the present inventive compositions include ascorbic acid, fumaric acid, malic acid, alpha tocopherol, ascorbic acid palmitate, butylated hydroxyanisole, propyl gallate, sodium ascorbate, sodium metabisulfite, and mixtures thereof.

Non-limiting examples of specific preservatives useful in the present inventive compositions include methylparaben, benzalkonium chloride, propylparaben, benzoic acid, EDTA, phenolic acid, sorbic acid, benzyl

alcohol, isopropyl alcohol, benzethonium chloride, bronopol, butylparaben, cetrimide, chlorhexidine, chlorobutanol, chlorocresol, cresol, ethylparaben, glycerol, imidurea, phenol, phenoxyethanol, phenylethyl alcohol, potassium sorbate, propylene glycol, sodium benzoate, sodium propionate, sorbic acid, thimerosol, and mixtures thereof. A particularly preferred preservative in this regard is methylparaben.

Non-limiting examples of specific emollients useful in the present inventive compositions include myristyl lactate, isopropyl palmitate, light liquid paraffin, cetearyl alcohol, lanolin, mineral oil, petrolatum, ceryl esters wax, cholesterol, glycerol, glycerol monostearate, isopropyl myristate, lecithin, and mixtures thereof. Particularly preferred emollients in this regard are myristyl lactate, isopropyl palmitate, and light liquid paraffin.

Non-limiting examples of specific humectants useful in the present inventive compositions include glycerin, propylene glycol, sorbitol, and triacetin.

Non-limiting examples of specific fluid alkyl alcohols useful in the present inventive compositions include ethanol, isopropyl alcohol, octodecyl alcohol, propyl alcohol, butanol, and pentanol. A particularly preferred fluid alkyl alcohol in this regard is ethanol.

Non-limiting examples of specific thickening agents

useful in the present inventive compositions include cetyl alcohol, Carbomers, acrylates/C10-30 alkyl acrylate crosspolymers, hydroxyethylcellulose, hydroxypropylcellulose, polyethylene oxide, and mixtures thereof. Particularly preferred thickening agents in this regard are cetyl alcohol, Carbomer 940, and acrylates/C10-30 alkyl acrylate crosspolymer.

The pH modifiers useful in the present inventive compositions include acids, bases, and mixtures thereof. Preferred non-limiting examples of pH modifiers in this regard include acetic acid, acetylsalicyclic acid, ascorbic acid, boric acid, carbonic acid, citric acid, formic acid, ethanesulfonic acid, fumaric acid, glycerophosphoric acid, hippuric acid, hydrochloric acid, maleic acid, methanesulfonic acid, nitrous acid, oxalic acid, phosphoric acid, saccharin, sorbic acid, sulfuric acid, thiosulfuric acid, undecylenic acid, ethanolamine, triethanolamine, sodium carbonate, sodium acetate, sodium hydrogen phosphate, sodium dihydrogen phosphate, sodium citrate, sodium bicarbonate, sodium hydroxide, and mixtures thereof.

In a particularly preferred embodiment, the pH modifier contains a hydroxyl group. A most preferred pH modifier containing a hydroxyl group useful in the present inventive compositions is sodium hydroxide.

Methods of Treatment

The present inventive subject matter additionally pertains to a method of treating a steroid responsive dermatosis in a mammal, comprising topically administering to a mammal in need thereof a therapeutically effective amount of a pharmaceutical composition suitable for topical administration comprising:

about 1 to about 30% by weight of an α-hydroxy acid or a pharmaceutically acceptable salt thereof having a purity of at least 90% and a concentration of degradation product(s) less than about 10% of the starting concentration of said α-hydroxy acid;

about 0.05 to about 2.0% by weight of prednicarbate or a pharmaceutically acceptable salt thereof having a purity of at least 90% and a concentration of degradation product(s) less than about 10% of the starting concentration of said prednicarbate; and

about 0.5 to about 10% by weight of a pyrrolidone carboxylate salt.

Several specific steroid responsive dermatoses may be treated according to the present inventive methods. Examplary among these dermatoses are contact dermatitis, eczema, atopic dermatitis, ichthyosis, psoriasis, xeroderma, seborrheic dermatitis, nummular dermatitis, stasis dermatitis, lichen simplex chronicus,

dermatophytids, candidiasis, scabies, pityriasis rosea, lichen planus, pityriasis rubra pilaris, bullous pemphigoid, miliaria, acute and chronic eczema, lupus erythematosis, photoallergic reactions, pruritis, and combinations thereof. Other steroid responsive dermatoses known to those of ordinary skill in the art are further contemplated as within the scope of the present inventive subject matter.

The steroid responsive dermatosis treated according to the present inventive methods can have a variety of causes. Several non-limiting examples of such causes include hypersensitivity, IgE mediation, anti-membrane antibody, immune complex disease, cell mediated immunity, and combinations thereof.

The steroid responsive dermatosis may also be caused by an insult to a tissue of the mammal having the dermatosis. Several non-limiting examples of such insults include a physical insult, a chemical insult, an environmental insult, a topically mediated insult, an internally mediated insult, and combinations thereof.

Additionally, said steroid responsive dermatosis may be a secondary physiologic response to a primary disease. Several non-limiting examples of such primary diseases causative of the steroid responsive dermatosis include an infection, an allergic response, a hyperproliferative disorder, an immunologic disorder, a metabolic disorder,

a drug induced response, a disorder related to proper or improper organ function, and combinations thereof.

The steroid responsive dermatosis may cause a variety of symptoms in the mammal afflicted therewith. Non-limiting examples of possible symptoms include inflammation, redness, tissue disruption, tissue deformation, exudates, crusting, pain, pruritis, and mixtures thereof.

In addition to treating steroid responsive dermatosis, the present inventive methods also contemplate using the inventive compositions described herein for treating diseases tissue in a mammal.

Methods of Production

The present inventive subject matter further relates to a process for preparing a pharmaceutical composition suitable for topical administration comprising an emulsion, said process comprising:

1) preparing an oil phase comprising an oily material selected from the group consisting of mineral oil, petrolatum, petroleum derivatives, fatty acids, fatty acid derivatives, fatty alcohols, fatty alcohol derivatives, paraffins, and mixtures thereof and at least two emulsifiers;

2) preparing an aqueous phase comprising an α-hydroxy acid or a pharmaceutically acceptable salt thereof having a purity of at least 90% and a

concentration of degradation product(s) less than about 10% of the starting concentration of said α-hydroxy acid and a pyrrolidone carboxylate salt;

3) adjusting the pH of said aqueous phase to a range of about 3.0 to about 6.0.

4) adding said oil phase to said aqueous phase while mixing at a temperature of about 55 to about 85 ^{0}C to obtain a homogenous emulsion;

5) cooling said emulsion to a temperature of about 25 to about 45 ^{0}C;

6) solubilizing prednicarbate or a pharmaceutically acceptable salt thereof having a purity of at least 90% and a concentration of degradation product(s) less than about 10% of the starting concentration of said prednicarbate in a lower alkyl alcohol and dispersing said prednicarbate throughout said emulsion; and

7) recovering a topical emulsion pharmaceutical composition.

In a preferred embodiment of the present inventive subject matter, the oil phase is prepared by mixing an oily material and at least two emulsifiers at a temperature of about 55 to about 85 ^{0}C. In a particularly preferred embodiment, the oil phase is prepared by further mixing a thickening agent, an emollient, and a preservative with the oily material and

the at least two emulsifiers.

In another preferred embodiment of the present inventive subject matter, the aqueous phase is prepared by first mixing a preservative followed by a polymer thickening agent in purified water at a temperature of about 55 to about 85 ^{0}C before adding an α-hydroxy acid or a pharmaceutically acceptable salt thereof and a pyrrolidone carboxylate salt. Once these ingredients are mixed, a pH modifier is added to the aqueous phase to ensure a pH of about 3.0 to about 6.0, preferably about 4.0 to about 5.0. In a particularly preferred embodiment, the pH is adjusted by adding sodium hydroxide to the aqueous phase. This pH represents the final pH of the composition. It is necessary to adjust the pH of the aqueous phase before addition of the oil phase to ensure that the oil phase does not intermingle with the aqueous phase, destroying the emulsion, during addition of the pH modifier.

In a particularly key aspect of the present inventive process, the emulsion is cooled from a temperature of about 55 to about 85 ^{o}C to a temperature of about 25 to about 45 ^{o}C before the prednicarbate is dispersed therein. This cooling step is particularly important because a substantial amount of prednicarbate degradation products will form at temperatures above 63 ^{o}C. Accordingly, it is necessary to cool the emulsion

before adding the prednicarbate to maintain the high prednicarbate purity and low amount of prednicarbate degradation products essential to the present inventive compositions.

Further contemplated as within the scope of the present inventive subject matter are pharmaceutical compositions produced according to the above-described process, wherein the α-hydroxy acid and the prednicarbate in said compositions each maintain a purity of at least 90% and a concentration of degradation product(s) less than about 10% of the starting concentration of the α-hydroxy acid and the prednicarbate. If produced according to the present inventive process, these compositions exhibit chemical and physical stability suitable for topical administration.

The compositions produced according to these processes can further be used in a lotion, cream, ointment, shampoo, or other pharmaceutically acceptable topical dosage form. These compositions can be placed in a suitable containment vessel comprising a product contact surface composed of a material selected from the group consisting of glass, plastic, steel, stainless steel, aluminum, Teflon, polymeric structure, ceramic structure, alloys, and mixtures thereof. These containment vessels are used to facilitate manufacturing, handling, processing, packaging, storage, and

administration of said composition.

Dosage

Appropriate dosage levels for the active agents contemplated in the present inventive subject matter are well known to those of ordinary skill in the art. Dosage levels on the order of about 0.001 mg to about 5,000 mg per kilogram body weight of the active therapeutic compounds or compositions are known to be useful in the treatment of the diseases, disorders, and conditions contemplated in the present invention. Typically, this effective amount of the active therapeutic agents will generally comprise from about 0.1 mg to about 100 mg per kilogram of patient body weight per day. Moreover, it will be understood that this dosage of active therapeutic agents can be administered in a single or multiple dosage units to provide the desired therapeutic effect. If desired, other therapeutic agents can be employed in conjunction with those provided by the present inventive subject matter.

As previously discussed, excessive use of hydrocortisone is well-known to exhibit a variety of undesired side effects, including redness, blistering, peeling, thinning of the skin, and stretch marks. These hydrocortisone side effects are especially pronounced in children and those having sensitive skin. The present inventive compositions solve these art-recognized

problems since they contain the steroid prednicarbate, which is more easily tolerated by children and those having sensitive skin, rather than hydrocortisone. Accordingly, the present inventive compositions are especially formulated for pediatric use and for administration to sensitive skin. The present inventive compositions permit a greater frequency of administration and a greater amount of drug to be delivered to children and those with sensitive skin due to inclusion of the steroid prednicarbate rather than hydrocortisone.

The present inventive compositions may be given in a single or multiple doses daily. In a preferred embodiment, the present inventive compositions are given from one to three times daily. Starting with a low dose twice daily and slowly working up to higher doses if needed is a preferred strategy. The amount of active ingredients that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated, the nature of the disease, disorder, or condition, and the nature of the active ingredients.

It is understood, however, that a specific dose level for any particular patient will depend upon a variety of factors well known in the art, including the activity of the specific compound employed; the age, body weight, general health, sex and diet of the patient; the

time of administration; the rate of excretion; drug combination; the severity of the particular disorder being treated; and the form of administration. One of ordinary skill in the art would appreciate the variability of such factors and would be able to establish specific dose levels using no more than routine experimentation.

The optimal pharmaceutical formulations will be determined by one skilled in the art depending upon considerations such as the particular drug or drug combination and the desired dosage. See, for example, "Remington's Pharmaceutical Sciences", 18th ed. (1990, Mack Publishing Co., Easton, PA 18042), pp. 1435-1712, the disclosure of which is hereby incorporated by reference. Such formulations may influence the physical state, stability, rate of *in vivo* release, and rate of *in vivo* clearance of the therapeutic agents.

EXAMPLES

The following examples are illustrative of the present inventive subject matter and are not intended to be limitations thereon. All polymer molecular weights are mean average molecular weights. All percentages are based on the percent by weight of the final delivery system or formulation prepared unless otherwise indicated and all totals equal 100% by weight.

EXAMPLE 1

The following example illustrates the preparation of a lotion of the present inventive subject matter:

	% W/W
Purified Water	64.467
Cetyl Alcohol	0.590
Stearyl Alcohol (and) Ceteareth-20	2.160
Carbomer 940	0.600
Glyceryl Stearate PEG-100/ Glyceryl Stearate	1.4200
Sodium Hydroxide	2.000
Myristyl Lactate	0.800
Methyl paraben	0.050
Isopropyl Palmitate	3.920
Sodium pyrrolidone carboxylate	5.200
Propylparaben	0.150
Light liquid paraffin	9.520
Lactic acid	5.573
Anhydrous ethanol	3.000
Acrylates/C10-30 Alkyl Acrylate Crosspolymer	0.300
Prednicarbate	0.250
	100.0%

Preparation of the composition:

1. Combine the materials cetyl alcohol, myristyl

lactate, light liquid paraffin, isopropyl palmitate, propylparaben, stearyl alcohol (and) Ceteareth-20, and Glyceryl Stearate PEG-100/Glyceryl Stearate, mix and heat to 70 °C ± 1 °C to form an oil phase.

2. Heat purified water to 70 °C ± 1 °C, add methylparaben and mix until clear. Add Carbomer 940 and Acrylates/C10-30 Alkyl Acrylate Crosspolymer and mix. Add sodium pyrrolidone carboxylate and lactic acid and mix to form an aqueous phase. In a separate vessel dissolve sodium hydroxide in water and add to the aqueous phase.

3. Add the oil phase to the aqueous phase and mix, maintaining the temperature of 70 °C ± 1 °C to form an emulsion. Cool to 35 °C with mixing. Solubilize prednicarbate in anhydrous ethanol, add to the emulsion, and mix.

EXAMPLE 2

A patient is suffering from contact dermatitis. A pharmaceutical composition of the present inventive subject matter is topically administered to the patient. It would be expected that the patient would improve his/her condition or recover.

EXAMPLE 3

A patient is suffering from eczema. A pharmaceutical composition of the present inventive subject matter is topically administered to the patient.

It would be expected that the patient would improve his/her condition or recover.

EXAMPLE 4

A patient is suffering from atopic dermatitis. A pharmaceutical composition of the present inventive subject matter is topically administered to the patient. It would be expected that the patient would improve his/her condition or recover.

EXAMPLE 5

A patient is suffering from ichthyosis. A pharmaceutical composition of the present inventive subject matter is topically administered to the patient. It would be expected that the patient would improve his/her condition or recover.

EXAMPLE 6

A patient is suffering from psoriasis. A pharmaceutical composition of the present inventive subject matter is topically administered to the patient. It would be expected that the patient would improve his/her condition or recover.

EXAMPLE 7

A patient is suffering from xeroderma. A pharmaceutical composition of the present inventive subject matter is topically administered to the patient. It would be expected that the patient would improve his/her condition or recover.

EXAMPLE 8

A patient is suffering from seborrheic dermatitis. A pharmaceutical composition of the present inventive subject matter is topically administered to the patient. It would be expected that the patient would improve his/her condition or recover.

EXAMPLE 9

A patient is suffering from nummular dermatitis. A pharmaceutical composition of the present inventive subject matter is topically administered to the patient. It would be expected that the patient would improve his/her condition or recover.

EXAMPLE 10

A patient is suffering from stasis dermatitis. A pharmaceutical composition of the present inventive subject matter is topically administered to the patient. It would be expected that the patient would improve his/her condition or recover.

EXAMPLE 11

A patient is suffering from lichen simplex chronicus. A pharmaceutical composition of the present inventive subject matter is topically administered to the patient. It would be expected that the patient would improve his/her condition or recover.

EXAMPLE 12

A patient is suffering from dermatophytids. A

pharmaceutical composition of the present inventive subject matter is topically administered to the patient. It would be expected that the patient would improve his/her condition or recover.

EXAMPLE 13

A patient is suffering from candidiasis. A pharmaceutical composition of the present inventive subject matter is topically administered to the patient. It would be expected that the patient would improve his/her condition or recover.

EXAMPLE 14

A patient is suffering from scabies. A pharmaceutical composition of the present inventive subject matter is topically administered to the patient. It would be expected that the patient would improve his/her condition or recover.

EXAMPLE 15

A patient is suffering from pityriasis rosea. A pharmaceutical composition of the present inventive subject matter is topically administered to the patient. It would be expected that the patient would improve his/her condition or recover.

EXAMPLE 16

A patient is suffering from lichen planus. A pharmaceutical composition of the present inventive subject matter is topically administered to the patient.

It would be expected that the patient would improve his/her condition or recover.

EXAMPLE 17

A patient is suffering from pityriasis rubra pilaris. A pharmaceutical composition of the present inventive subject matter is topically administered to the patient. It would be expected that the patient would improve his/her condition or recover.

EXAMPLE 18

A patient is suffering from bullous pemphigoid. A pharmaceutical composition of the present inventive subject matter is topically administered to the patient. It would be expected that the patient would improve his/her condition or recover.

EXAMPLE 19

A patient is suffering from miliaria. A pharmaceutical composition of the present inventive subject matter is topically administered to the patient. It would be expected that the patient would improve his/her condition or recover.

EXAMPLE 20

A patient is suffering from acute eczema. A pharmaceutical composition of the present inventive subject matter is topically administered to the patient. It would be expected that the patient would improve his/her condition or recover.

EXAMPLE 21

A patient is suffering from chronic eczema. A pharmaceutical composition of the present inventive subject matter is topically administered to the patient. It would be expected that the patient would improve his/her condition or recover.

EXAMPLE 22

A patient is suffering from lupus erythematosis. A pharmaceutical composition of the present inventive subject matter is topically administered to the patient. It would be expected that the patient would improve his/her condition or recover.

EXAMPLE 23

A patient is suffering from photoallergic reactions. A pharmaceutical composition of the present inventive subject matter is topically administered to the patient. It would be expected that the patient would improve his/her condition or recover.

EXAMPLE 24

A patient is suffering from pruritis. A pharmaceutical composition of the present inventive subject matter is topically administered to the patient. It would be expected that the patient would improve his/her condition or recover.

The inventive subject matter being thus described, it will be apparent that the same may be modified or

varied in many ways. Such modifications and variations are not to be regarded as a departure from the spirit and scope of the inventive subject matter, and all such modifications and variations are intended to be included within the scope of the following claims.